BIGGER Correlative Sciences Workshop
Goals of the Workshop

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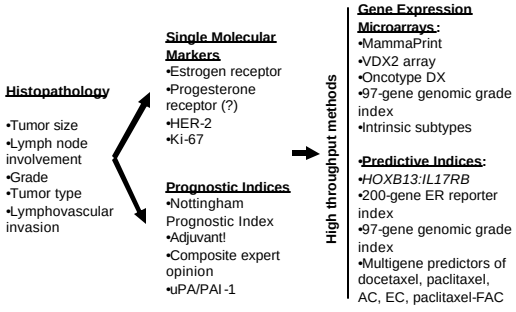
Why do we need biomarkers?

- To determine prognosis
- To identify distinct disease subgroups
- To predict benefit from or resistance to treatment
- To improve classifications
- To compare trial results
- To identify novel targets
- To improve diagnosis
- To enrich patient populations for a desirable characteristic

Historical Evolution of Biomarkers for Breast Cancer



Inefficient and Ineffective Development of Biomarkers

- Over the past four decades, more than 300 biomarkers have been proposed and supported by at least one peer-reviewed publication
- We only use Histopathology, ER, HER2, Adjuvant! and Oncotype DX in routine practice: 5 o >300!!!

Obstacles for Effective Biomarker Development

- Assessment of biomarkers is usually (always?) an afterthought in therapeutic clinical trials
- Initial reports are irreproducible
- No validated assay
- Assay requires hard-to-get biological sample (fresh, large quantity, etc.)
- Biological hypothesis uncertain or questionable
- Absence of "deep pockets" to assess and validate proposed biomarker
- Competing research priorities
- Necessary biospecimens unavailable
- Relevant technology unavailable

High Bar for Predictive Tests

- Must enrich patient population with candidates likely to respond/benefit
  - What level of enrichment is clinically useful?
- Must not exclude patients likely to benefit
  - What is the acceptable level of false negative assays? 10%? 5%? 1%?
  - Can we perform clinical trials to rule out such low probabilities of false negative results?

This Symposium Should Start to Overcome those Obstacles

- All participants have a major interest in biomarker development
- It is widely accepted that the development of molecular diagnostics must accompany the development of molecular therapeutics.
- There is clear commitment from investigators, NCI and industry to improve the process of discovery and validation of biomarkers
- Our understanding of cancer biology is markedly enhanced
- NA Cooperative groups have a large collection of annotated, prospectively collected biological samples
- High throughput technologies widely available
- Multiple candidate prognostic or predictive markers/indices available for validation
- There are funds earmarked for biomarker discovery and validation

Objectives

- 1. To develop consistent strategies and planning for evaluation of clinical utility of tumor markers by breast cancer cooperative groups.
- 2. To specifically address two separate markers as examples:
  - a. Intrinsic subtype (basal, luminal A, B, etc) signatures as prognostic factors
  - b. Chemotherapy predictive signatures
- 3. To review currently available technologies for high throughput assays for DNA, RNA, and/or protein abnormalities designed to identify new signatures for prognosis or prediction

Should we profile all biospecimens from the cooperative groups clinical trials?

Or should we wait until technology is perfected/improved?

"Perfect" is the Worst Enemy of "Good"

What the Cooperative Groups Can (Should?) Do Going Forward

- Improve and standardize pre-analytic handling of biospecimens:
  - Time from devascularization to preservative
  - Type and time in preservative
- Explicit focus on the development of high quality biomarkers
- Strategic choices of clinically relevant questions
- Strategic choices of discovery and validation samples
- Prioritizing questions, resources and biostatistical support
- Start exploring other emerging technologies: proteomics, metabolomics, etc.

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Discussion of Specific New Trials/Studies of 2 new assays

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New Prognostic and Predictive Assays

- Overview of Goals for each assay highlighting issues brought forward from previous day's discussions:
  - Definition
  - Potential Utilities
  - Assays
    - Reproducibility, CV
    - Sensitivity, specificity, PPV, NPV
  - Specific Studies